UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/749,709	12/27/2000	Chengyu Liu	19412-1773001	6178

7590 02/10/2004

Chris A. Caseiro
Pierce Atwood
One Monument Square
Portland, ME 04101

EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,709	LIU ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2000* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0601*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-8 and 12, in the reply received on 3/10/03 is acknowledged. The traversal is on the ground(s) that it would not be undue to search and examine the claims of all groups with respect to all non-human animals. This is not found persuasive because it is maintained that each of inventions I-III requires a separate search status. In particular it is maintained the methods of inventions I-III are distinct each from the other, as each requires different technical considerations and materially different products. For example, the methods of Group I embrace pronuclear injection, the methods of Group II embrace homologous recombination in ES cells, and the methods of Group III embrace nuclear transfer. Thus, as the methods of Inventions I-III are materially different, each having a different mode of operation, it is finally maintained that the inventions embrace divergent methods of creating transgenic non-human animals, which are separately searched.

The requirement is still deemed proper and is therefore made FINAL.

Note: As per Applicant's request, the search and examination of the claims of Invention I will be extended to all species of non-human animals.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final

action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 9-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Drawings

New corrected drawings are required in this application because Figure 1 is handwritten. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

Claims 1, 2 and 8 are objected to as they embrace non-elected inventions.

Claim 1 is objected to because of the following informalities: the term "result" in line 2 should be "results". Appropriate correction is required.

Claim 1 is objected to as identifiers a, b, and c are followed by periods.

Claim 5 is objected to because hsp 70.1 and wnt.gene have internal periods.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to method of producing transgenic animals whose offspring have altered sex ratios.

The specification discusses that the invention features a method of controlling the sex of transgenic offspring. See page 2. The specification discusses that the invention features a method of altering the sex ratio of transgenic offspring by expression of a toxin in spermatids containing a particular sex chromosome. See pages 2-4 and also throughout the specification. The specification contemplates that such a method may, for example be useful in controlling the sex of farm animals, as one sex may be advantageous for producing products such as meat, milk, egg and wool. See pages 1 and 3. However, the specification fails to provide any relevant teachings, specific guidance, or working examples with regard to generation of transgenic offspring having altered sex ratios, wherein the offspring are produced from transgenic male animals, from which a spermatid having a particular sex chromosome has been

eliminated by specific expression of a toxin. Furthermore, the specification fails to even describe any offspring having altered sex ratios produced by the claimed methods. Thus, as enablement requires the specification to teach how to make and use the claimed invention without undue experimentation, the specification fails provide guidance enabling the claimed methods for the production of transgenic offspring having altered sex ratios.

As a first issue, the claims embrace the creation of transgenic animals that express a toxin, wherein the nucleotide sequence encoding the toxin has been inserted into one of the sex chromosomes and wherein expression of the toxin results in elimination of spermatids comprising either sex chromosome. As the specification fails to provide any relevant teachings or guidance with regard to the production of such transgenic, as embraced by the claims, one of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic animals that comprise and express any heterologous nucleotide sequence encoding a toxin. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype, in particular expression of the toxin such that a spermatid comprising either sex chromosome is eliminated. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic non-human mammals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype, particularly expression of toxin resulting in elimination of a spermatid comprising a particular sex chromosome. For instance, the level and specificity of

expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); *e.g.*, specific promoters, presence or absence of introns, *etc.* As such guidance is lacking in the instant specification, it fails to feature any correlation between the expression of any heterologous nucleotide sequence encoding a toxin in any host animal, and, thus, a specific resulting phenotype, particularly elimination of a spermatid comprising a particular sex chromosome.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic animals is not predictable and varies according to the particular host species and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human

growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of transgenic animals comprising any heterologous nucleotide sequence encoding a toxin, it would have required undue experimentation to predict the results achieved in any one host animal comprising and expressing any heterologous nucleotide sequence encoding a toxin, the levels of the

expression product, the consequences of that production, and therefore, the resulting phenotype of elimination of a spermatid comprising a particular sex chromosome.

As a second issue, the claims embrace embodiments directed to homologous recombination. The elected invention is directed to pronuclear injection as the means of producing the transgenic animals. Pronuclear injection relies on random integration of a transgene into the genome of an animal. The specification has failed to provide guidance correlating to targeting of a transgene to specific loci of the sex chromosomes using methodology that relies on random transgene integration. It is unpredictable if random integration of a transgene would enable targeting to specific loci of the sex chromosomes. Given the lack of guidance with respect to targeting of specific sex chromosome loci by random integration provided by the instant specification it would have required undue experimentation to practice the claimed invention.

As a final issue, the claims embrace a transgene (and an animal comprising it) comprising optional loxP sites. When the loxP sites are not included in the claimed invention, the required step of introducing Cre recombinase activity into an animal of the invention appears to have apparent function or purpose. Moreover, when loxP sites are not part of the invention, it appears that toxin expression would be ubiquitous and could result in embryonic lethality of founder animals or in elimination of sperm production of founder animals. Accordingly, the claims do not appear enabled for production of transgenic animals having altered sex ratios when loxP sites are not part of the invention. It would have required undue experimentation to practice the invention as claimed when loxP sites are excluded from the invention.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic animal comprising altered sex ratios, the lack of direction or guidance provided by the specification for the production of transgenic animals having altered sex ratios by way of the methods as claimed, the absence of working examples for the demonstration or correlation to the production of transgenic animals having altered sex ratios by way of the claimed methods; the unpredictable state of the art with respect to transgene expression and resulting phenotype, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claims 1-8 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to method of producing transgenic animals whose offspring have altered sex ratios.

The nucleotide sequences that encode all toxins, other than Herpes simplex virus thymidine kinase (HSV-TK), and variants thereof (including mutated or truncated forms of HSV-TK) that when expressed interfere with sperm's ability to undergo fertilization, wherein the expression products thereof (mRNA or protein) act in a no-random diffusion fashion among interconnected spermatids, encompassed within the genus of nucleotide

molecules encoding toxins have not been disclosed. Based upon the prior art there is expected to be variation among the species of cDNA, which encode toxins, because the sequence of toxin cDNAs would be expected to vary. The specification describes a nucleotide sequence encoding Herpes simplex virus thymidine kinase (HSV-TK), which when expressed interferes with sperm's ability to fertilize and diffuses in a limited manner among the inter-connected spermatids, and does not disclose nucleotide sequence encoding all other toxins embraced by the claims. There is no evidence on the record of a relationship between the structure of an HSV-TK cDNA and the other nucleotide sequence encoding toxins embraced by the claims that would provide any reliable information about the structure of other toxin encoding cDNAs within the genus. There is no evidence on the record that the HSV-TK cDNA had a known structural relationship to any other toxin encoding cDNA sequences, which when expressed interfere with sperm's ability to fertilize and diffuse in a limited manner among the inter-connected spermatids ; the specification discloses only an HSV-TK cDNA; the art indicated that there is variation between toxin encoding cDNA sequences. There is no evidence of record that would indicate that any of the variants of HSV-TK embraced by the claims, even have biological activity of interfering with sperm's ability to fertilize and diffusing in a limited manner among the inter-connected spermatids. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because an HSV-TK cDNA sequence is not representative of the claimed genus. Consequently, since Applicant was in possession of only the HSV-TK cDNA

and since the art recognized variation among the species of the genus of cDNAs that encode toxins, the HSV-TK cDNA was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of toxin encoding cDNAs as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to method of producing transgenic animals whose offspring have altered sex ratios.

The nucleotide sequences for targeting sex chromosomes (X, Y, Z, and W), other than the mouse Hrpt gene and the mouse Tspy pseudogene for targeting the mouse X and Y-chromosomes respectively, encompassed within the genus of sex-linked nucleotide molecules have not been disclosed. Based upon the prior art there is expected to be variation among the species of nucleotide sequences, located on sex chromosome, which can be targeted because the nucleotide sequences would be expected to vary. The specification describes nucleotide sequences of the mouse Hrpt

gene and mouse Tspy pseudogene but does not disclose other the nucleotide sequences located sex chromosomes embraced by the claims. There is no evidence on the record of a relationship between the structures of mouse Hrpt and mouse Tspy cDNAs and the other nucleotide sequences located on sex chromosomes embraced by the claims that would provide any reliable information about the structure of other nucleotide sequences within the genus. There is no evidence on the record that the mouse Hrpt and mouse Tspy cDNAs had a known structural relationship to any other sex-linked DNA sequences, which when disrupted will not cause abnormal phenotype in transgenic animals; the specification describes only mouse Hrpt and mouse Tspy sequences; the art indicated that there is variation among sex-linked nucleotide sequences. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by members of the genus, because mouse Hrpt and mouse Tspy nucleotide sequences are not representative of the claimed genus. Consequently, since Applicant was in possession of only the mouse Hrpt and mouse Tspy nucleotide sequences and since the art recognized variation among the species of the genus of sex-linked nucleotide sequences, the mouse Hrpt gene and the mouse Tspy pseudogene were not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of sex-linked nucleotide sequences for targeting nucleotide sequences of sex chromosomes as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and

do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "such as", in line 5 of step a, renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Moreover, claim 1 is replete with recitations in parentheses, which are interpreted to mean "such as". Such are indefinite as previously discussed. Appropriate correction is required. Claims 2-7 and 12 depend from claim 1.

Claim 1 is incomplete as written. The claim is directed to a method for producing transgenic animals whose somatic and germ cells contain one or more transgenes, wherein expression of the transgenes results in alteration of the sex ratio of the offspring of said animals. The steps relating to creation of transgenic animals are not included in the claim. Moreover, the steps of the method do not relate to the goal of the preamble in a positive process. For example, the steps of the method do not result in

alteration of offspring's sex ratio. Appropriate correction is required. Claims 2-7 and 12 depend from claim 1.

Claim 1 is indefinite as written. The claim requires identifying at least one transgenic animal with desirable reproduction feature, specifically, alteration of offspring's sex ratio. It is not understood how a transgenic animal can possess a feature such as alteration of offspring's sex ratio. It does not appear that alteration of offspring's sex ratio is a feature that can be possessed by a transgenic animal. Appropriate correction is required. Claims 2-7 and 12 depend from claim 1.

Claim 1 recites the limitation "the toxin gene" in step a, line 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 recites the limitation "the toxin transgene" in step a, line 9. There is insufficient antecedent basis for this limitation in the claim. Claims 2-7 and 12 depend from claim 1.

Claim 1 is indefinite as written. Step b is directed to a DNA sequence encoding a toxic gene. The claim is indefinite because DNA sequences normally encode proteins rather than genes. Neither the specification nor the art has defined a DNA sequence that encodes a gene. In addition, the specification has not provided a definition of what is meant by "toxic gene" (see claim 3 as well). As written, it appears the gene sequence itself is toxic. Appropriate correction is required. Claims 2-7 and 12 depend from claim 1.

Claim 1 is indefinite as written. Lines 1-2 of the claim are directed to a method for producing transgenic animals whose somatic/germ cells contain one or more

transgenes. The term "somatic/germ cells" is interpreted to read as somatic and/or germ cells. Therefore it is not apparent if the claim embraces somatic and germ cells or only somatic or germ cells. Appropriate correction required. Claims 2-7 and 12 depend from claim 1.

Claim 1 is indefinite as written. The phrase "sperm's ability to undergo fertilization" is not understood because neither the specification nor the art have defined a process in which sperm undergo fertilization. Normally, it is expected that an oocyte undergoes fertilization via sperm. Appropriate correction is required.

Claim 1 is indefinite as written. The claim embraces an expression regulatory sequence functional in a post-meiotic spermatogenesis-specific way. The claim is indefinite because it is not understood what is meant by "functional in a post-meiotic spermatogenesis-specific way". The specification has not provided a definition of how a regulatory sequence is functional in a post-meiotic spermatogenesis-specific way. It appears Applicants are intending to claim a post-meiotic spermatogenesis-specific regulatory sequence. Appropriate correction is required.

Claim 2 is indefinite as written. The claim embraces animals that are unisexual flower plants. Neither the specification nor the art has defined an animal that is a plant. Appropriate correction is required.

Claim 3 is indefinite as written. The claim embraces a transgene selected from the group consisting of Herpes Simplex Virus thymidine kinase gene, its mutated or truncated genes and any other toxic genes. The claim is indefinite because the transgene was previously defined in claim 1, from claim 3 depends, as comprising a

regulatory sequence and a DNA sequence encoding a toxic gene. Accordingly, given the definition of transgene recited in the claims it is not understood how the transgene can be selected from the group consisting of Herpes Simplex Virus thymidine kinase gene, its mutated or truncated genes and any other toxic genes. Appropriate correction is required.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation its mutated or truncated genes and any other toxic genes, and the claim also recites Herpes Simplex Virus thymidine kinase gene, which is the narrower statement of the range/limitation.

Claim 3 is indefinite as written. The claim embraces Herpes Simplex Virus thymidine kinase gene and its mutated or truncated genes. However, the phrase "its

mutated or truncated genes" has no apparent meaning. It is not known or understood what are mutated or truncated genes of Herpes Simplex Virus thymidine kinase gene. The specification has not provided a definition to that end.

In addition, claim 3 is indefinite for reciting the following language: "toxic genes with characters", "its expression can interfering", "mRNA/protein products act in a no-random diffusion", and "mRNA/protein products". These phrases render the claim confusing and indefinite as no clear meaning of the claim language is apparent. Also, in steps a and b it is not understood what the term "its" is referring to. Appropriate correction is required.

Claim 3 is indefinite as written. The phrase "sperm's ability to undergo fertilization" is not understood because neither the specification nor the art have defined a process in which sperm undergo fertilization. Normally, it is expected that an oocyte undergoes fertilization via sperm. Appropriate correction is required.

Claim 4 recites the limitation "the offspring's desirable sex percentage of said transgenic animals" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 is confusing as written. The phrase "the offspring's desirable sex percentage of said transgenic animals is from 50% to 100%" does not have a clear meaning. The claim is confusing because it appears the offspring would produce the transgenic animals whereas independent claim 1, from which the instant claim depends, appears to read on offspring produced by the transgenic animals. Appropriate correction is required.

Claim 5 recites the limitation "said post-meiotic spermatogenesis specific promoter" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 5 recites the broad recitation any promoter, which can trigger post-meiotic expression of said transgenes, and the claim also recites a promoter from a Herpes Simplex Virus thymidine kinase gene, which is the narrower statement of the range/limitation.

Claim 5 is indefinite as written. The claim embraces post-meiotic spermatogenesis-specific promoters. However, the promoters listed are not all spermatogenesis-specific.

Claim 6 recites the limitation "said the DNA sequence for X-chromosome specific targeting" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 is indefinite as written. The phrase "said the DNA sequence" is confusing. Appropriate correction is required.

Claim 7 recites the limitation "said the DNA sequence for Y-chromosome specific targeting" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the post-meiotic spermatogenesis-specific promoter" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the transgene that disrupts sperm's function" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the toxin gene" in step 3, lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 is indefinite as written. Step 2 is directed to a DNA sequence encoding a toxic gene. The claim is indefinite because DNA sequences normally encode proteins rather than genes. Neither the specification nor the art has defined a DNA sequence that encodes a gene. In addition, the specification has not provided a definition of what is meant by "toxic gene". As written, it appears the gene sequence itself is toxic. Appropriate correction is required.

Regarding claim 8, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Moreover, claim 8 is replete with recitations in parentheses, which are interpreted to mean "such as". Such are indefinite as previously discussed. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Silversides et al (US 5,596,089).

The claims are directed to method of producing transgenic animals whose offspring have altered sex ratios.

Silversides et al teach methods of altering the sex ratios of transgenic offspring comprising: 1) preparing a transgene comprising a spermatogenesis-specific promoter (the SRY promoter) operably linked to a nucleotide sequence encoding a toxin (Diphtheria A chain toxin), wherein loxP sequences flanking an intervening sequence are positioned between the promoter and the toxin gene as they have been inserted into the transgene immediately downstream of the transcriptional start site of the Diphtheria A toxin gene; 2) creating transgenic animals comprising the above described transgene,

by pronuclear injection (this aspect of the claim is anticipated as the elected invention embraces pronuclear injection as the method for creating the transgenic animals and also because pronuclear injection relies on random integration of a transgene while the claim embraces targeted integration; random integration could result in transgene integration onto one of the sex chromosomes; it is noted that the targeting sequences are optional); and mating the said created transgenic animals with transgenic animals expressing Cre recombinase. In particular, Silversides discuss the creation of transgenic pigs. See columns 13-14 and also figures 9A-C. The transgenic offspring of Silversides would be expected to have altered sex ratios, particularly 50-100%. See Figure 9C.

Thus, the teachings of Silversides anticipate all of the instant claim limitations.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Eisel et al.

The claims are directed to method of producing transgenic animals whose offspring have altered sex ratios.

Eisel et al teach the creation of transgenic mice whose genomes comprise a transgene comprising a nucleotide sequence encoding tetanus toxin operably linked to a promoter functional in a post-meiotic spermatogenesis-specific way as expression was achieved in the testes. See page 3367 beginning in the paragraph bridging columns 1-2 and also Figure 3. The other embodiments of transgene recited in claim 1 are optional and steps b and c of claim 1 appear to require the optional transgene

embodiments. Since the mice of Eisel were created the claims are anticipated. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Thus, the teachings of Eisel et al anticipate all of the instant claim limitations.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER